

Signal Detection Report: Light therapy for non-seasonal depression

Signal Detection Report date

September, 2017

Key Findings

- Expert opinion: 6 out of 8 experts agreed that the original review's findings are no longer valid, and all of the experts provided new evidence
- Literature evidence: Qualitative and quantitative signals were identified

Summary Decision:

Authors

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Introduction

Previous research evaluating a cohort of published systematic reviews demonstrated that 7% of reviews were out of date by the time of publication, while as many as 23% went out of date within two years of being completed.[1] The utility of systematic review-based evidence depends on their remaining up-to-date. As such, the Cochrane Complementary Medicine Field and the Knowledge Synthesis group at the Ottawa Hospital Research Institute (OHRI) have determined a set of existing reviews of interest for which signal detection work using the Ottawa Method's qualitative/quantitative signal detection approach has been performed. [1]

The Ottawa method involves identification of qualitative and quantitative signals/triggers indicating the need of updating of a systematic review.[1] The Ottawa method has been used to assess the need for updating systematic reviews in the past.[1; 2] A graphical overview of our approach and application of the Ottawa signal detection method is provided in Appendix A, Figure 1 of this report. This work assessed potential triggers signifying the need for updating of six past Cochrane Complementary Medicine reviews. The conclusion as to whether or not each of the reviews is in need of updating was made based on the identification of qualitative and quantitative signals.

Methods

We contacted content experts to provide input on whether conclusions from the review were still valid, and if they were aware of any new evidence that could potentially signal the need for a review update. This process included the authors from the original review, and also reached out to the lead authors on the included studies of the review. If we did not find sufficient number of experts we then reached out to those who had responded and asked whether they could suggest possible content experts.

Summaries and conclusions were collected for each key question (or possibly key endpoint) within each review; this summary was shared with consulting experts when seeking their input regarding the findings, as well as when establishing the presence of updating triggers. See Appendix B for the survey sent to content experts.

Experts were asked their perspectives on the following features of each review: a) whether the conclusion is still valid in their own opinion (to be answered as yes/no/don't know); b) whether he/she is aware of new evidence published since the publication date of the review being assessed (with details if yes); and c) any additional information or perspectives to be shared. If an expert indicated an opinion that one or more conclusions of the review was out of date and/or provided specific evidence they felt was critical to the decision regarding updating, we verified it by assessing the evidence brought forward by the expert(s).

Experts were given 10 business days to respond. Two reminders were sent, and a conflict of interest disclosure statement was also sent to all experts that participated. The survey was kept open until a minimum of two clinical experts responded.

One reviewer screened the evidence provided by the content experts, and determined whether the studies met the inclusion criteria of the original review. Data was extracted by one reviewer. The identification of qualitative signals was carried out using the Ottawa method qualitative signals. The definition and categories of qualitative signals are presented in Appendix C.

An information specialist provided modified PRESS [3] evaluations of the original review's search strategy, commenting on databases, search dates and terminology. This information is provided in Appendix D in order to inform any future updating for the original review.

Expert Opinion

Out of 24 experts who were contacted, 8 experts agreed to participate in the survey. 6 stated that the findings from the original review were no longer valid, while the other 2 experts stated that the findings were still valid (however, one of those expert went on to comment that new evidence "could help to modify the magnitude of the effects" and that "adding 7 more studies, with hundreds of included patients, is likely to modify something. The review can then be considered incomplete, and must be re-written.")

Several experts commented on the findings of the original review:

"The analysis should be restricted to only those studies which follow elaborated in 1999 LT [light therapy] guidelines for: brightness (2500 lx); duration (30 minutes); field of view (convenient light boxes or light rooms - not small screen size devices, dawn simulators or light visors); light spectrum – fluorescent (or LED); and time of day (morning.)"

"There is much more positive evidence now and longer-term studies. The question of combinations of light, sleep phase advance, and sleep restriction (wake therapy) now arises from several studies reporting excellent results."

"I think the evidence for light for non-seasonal depression is stronger now than stated in the review due to a long number of studies some of which are of good quality; the quality of these studies vary very much. But some of them answer questions about side-effect and dosage issues."

"The result was mainly based on studies of less than 8 days of treatment, which might indicate a more rapid action than with antidepressant drugs. The short lasting of the studies and the absence of significant results do not indicate a more rapid action. Such formulation is fallacious. I think it also worth to be mentioned that the blinding of participants is an issue in these studies."

"The finding was fine for its time, but lacks the critical perspective of the important paper published by Lam et al in JAMA Psychiatry in 2015. This is considered to be a high quality paper. It is hard to overstate the importance of this paper in this area. Other useful papers have also been published in the past decade in this arena; Light therapy is equivalent in efficacy to medication treatment for non-seasonal depression, and in combination with pharmacotherapy may be superior to meds alone. This is a critical new advance."

Flow

248 studies were suggested by the experts as potential evidence that would invalidate the original review's findings. There was some overlap between the experts in terms of the studies that were put forth. An initial title screening of the 248 references was completed to identify randomized controlled trials (RCT) that potentially met the inclusion criteria of the original review.

23 references were assessed at full-text, and of those, 13 were included for qualitative assessment (see Appendix E for a list of the excluded references.) The majority of those that were excluded at full-text did not have a placebo comparator.

Signal Detection Results:

Findings of the original review

Overall Conclusion of the Review: "For patients suffering from non-seasonal depression, light therapy offers modest though promising anti depressive efficacy, especially when administered during the first week of treatment, in the morning, and as an adjunctive treatment to sleep deprivation responders. Hypomania as a potential adverse effect needs to be considered. Due to limited data and heterogeneity of studies these results need to be interpreted with caution." [4]

Further Details: "Twenty studies (49 reports) were included in the review. Most of the studies applied bright light as adjunctive treatment to drug therapy, sleep deprivation, or both. In general, the quality of reporting was poor, and many reviews did not report adverse effects systematically. The treatment response in the bright light group was better than in the control treatment group, but did not reach statistical significance. The result was mainly based on studies of less than 8 days of treatment, which might indicate a more rapid action than with antidepressant drugs. A wide range of durations and intensities of bright light were applied. High versus low daily duration and intensity of light did not show any superiority over each other. It also needs to be remembered that previous research has shown that these variables are interrelated and possibly confounding, i.e., the higher the intensity, the shorter the duration is effective. The review covered all forms of non-seasonal depression. The benefit of bright light in specific forms of depression and in various age groups was not possible to evaluate sufficiently. In particular, there was an absence of [randomized controlled trials] RCTs for more than four weeks of treatment." [4]

New findings:

Perera et al., 2016 is a systematic review that includes 20 RCTs (5 of which were included in the original review) and considered any type of light therapy. The study demonstrated beneficial effect for light therapy in non-seasonal depression score (SMD -0.41, 95% CI -0.64, -0.18). The authors report that, "this estimate was associated with significant heterogeneity ($I^2=60%$, $P=0.0003$) that was not sufficiently explained by subgroup analyses. There was also high risk of bias in the included trials limiting the study interpretation." The authors conclude that "the overall quality of evidence is poor due to high risk of bias and inconsistency. However, considering that light therapy has minimal side-effects and our meta-

analysis demonstrated that a significant proportion of patients achieved a clinically significant response, light therapy may be effective for patients with non-seasonal depression and can be a helpful additional therapeutic intervention for depression.” They conducted subgroup analyses and the stand alone light therapy showed statistically significant result (SMD -0.63, 95% CI -1, -0.25) but adjunctive light therapy did not (SMD -0.25, 95% CI -0.53, 0.03). Morning light therapy demonstrated greater effect (SMD -0.50, 95% CI -0.73, -0.27) compared to other time. Evening or mixed timed showed a non-significant result (SMD -0.08, 95% CI -0.70, 0.53). The treatment effect was shown to be effective in outpatients (SMD -0.50, 95% CI -0.81, -0.20) but not in inpatients (SMD -0.25, 95% CI -0.63, 0.13). When the analysis was restricted to a clinical response (50% reduction in depressive symptoms following treatment vs placebo), the meta-analysis displayed a statistically significant result (RR 0.67, 95% CI 0.54, 0.82, I² 21%) favoring light therapy. [5]

Al Karawi and Jubair 2016 describe a systematic review that includes 9 RCTs (2 of which are also included in the original review) and considered only bright light therapy as the primary intervention. The study demonstrated a significant reduction in depressive symptoms favoring bright light therapy (SMD -0.62, P<0.001, I² 37%), particularly when administered for 2-5 weeks (SMD -0.78, p<0.001, I²=0%), and as monotherapy (SMD -0.71, p<0.001, I²=18%) but insignificant association for perinatal depression (SMD -0.17, p>0.05, I² 44%). The authors report that “the overall heterogeneity of the included trials was moderate. The participants were not adequately blinded to the intervention. The sample size was small for certain subgroups. The long-term effect of BLT on depression was not explored.” The authors conclude that “BLT appears to be efficacious, particularly when administered for 2–5 weeks’ duration and as monotherapy. There is an obvious need to optimize the duration and intensity of exposure, the timing and the duration of treatment sessions.” [6]

Chojnacka et al., 2016 reports a RCT of 95 adults with a diagnosis of unipolar or bipolar depression. Patients were randomized to receive 30 minutes of morning BLT (10,000 lux, n = 52) or a sham negative ion generator (n = 43) for two weeks. The authors report that “after 14 days of treatment, a significant improvement was found in all groups (p <0.001). The subjects treated with BLT did not significantly differ in terms of improvement in HDRS-21 scores at the end point when compared to patients treated with placebo (p = 0.2). However, further analysis demonstrated significantly higher response (50% v. 27.9%, p = 0.02) and remission rates (28.8% v. 11.6%, p = 0.04) among patients treated with morning BLT when compared to placebo group. It should be noted that in the population of drug-resistant patients, BLT was more efficacious than placebo. There were no statistically significant differences between unipolar and bipolar disorders (p = 0.4).” The authors conclude that “although overall improvement in HDRS-21 scores were not superior in the BLT group, both response and remission rates were significantly higher among patients treated with BLT relative to those receiving the sham intervention. BLT was also more efficacious than placebo in the population of patients with drug-resistant depression.” [7]

Lam et al., 2015 reports a RCT that is included in both systematic reviews above. 122 patients were randomized into four arms: 32 in light monotherapy, 31 in fluoxetine monotherapy, 29 in combination therapy, and 30 in placebo. The authors reported that “the mean (SD) changes in MADRS score for the light, fluoxetine, combination, and placebo groups were 13.4 (7.5), 8.8 (9.9), 16.9 (9.2), and 6.5 (9.6),

respectively. The combination (effect size $[d] = 1.11$; 95%CI, 0.54 to 1.64) and light monotherapy ($d = 0.80$; 95%CI, 0.28 to 1.31) were significantly superior to placebo in the MADRS change score, but fluoxetine monotherapy ($d = 0.24$; 95%CI, -0.27 to 0.74) was not superior to placebo. For the respective placebo, fluoxetine, light, and combination groups at the end point, response was achieved by 10 (33.3%), 9 (29.0%), 16 (50.0%), and 22 (75.9%) and remission was achieved by 9 (30.0%), 6 (19.4%), 14 (43.8%), and 17 (58.6%). Combination therapy was superior to placebo in MADRS response ($\beta = 1.70$; $df = 1$; $P = .005$) and remission ($\beta = 1.33$; $df = 1$; $P = .02$), with numbers needed to treat of 2.4 (95%CI, 1.6 to 5.8) and 3.5 (95%CI, 2.0 to 29.9), respectively. All treatments were generally well tolerated, with few significant differences in treatment-emergent adverse events." The authors conclude that "bright light treatment, both as monotherapy and in combination with fluoxetine, was efficacious and well tolerated in the treatment of adults with nonseasonal MDD. The combination treatment had the most consistent effects." [8]

Niederhofer and Klitzing 2012 is a randomized crossover trial of 28 adolescents diagnosed with mild depressive disorder. Participants were randomized to receive either placebo for one hour per day (50 lux, $n = 14$) or bright light therapy for one hour per day (2500 lux, $n = 14$) for one week in the morning, and then crossed over to the other group for one week. There was a lead-in week and a follow-up of one week, for an entire study duration of 4 weeks. The authors report that "BDI scores were stable in the pre-treatment period, improved in group 1 during treatment significantly with placebo, and then during treatment with bright light and rose again after the following week. Group 2 dropped from an initial score equal to that of group 1 significantly during BLT and rose again during placebo treatment. In the post-treatment period, the score rose in both groups again up to the initial values. The authors conclude that "antidepressant response to bright light treatment in this age group was statistically superior to placebo." [9]

Lieverse et al., 2011 describes a RCT of 89 adults over 60 years of age with diagnosed non-seasonal major depression. Patients were randomized to receive 1-hour early morning BLT (bright light treatment, pale blue 7500 lux, $n = 42$) or placebo (dim red light, 50 lux, $n = 47$) daily for three weeks. The authors report that "intention-to-treat analysis showed Hamilton Scale for Depression scores to improve with BLT more than placebo from T0 to T1 (7%; 95% confidence interval, 4%-23%; $P=.03$) and from T0 to T2 (21%; 7%-31%; $P=.001$)." The authors conclude that "in elderly patients with MDD [major depressive disorder,]BLT improved mood...in addition, BLT produced continuing improvement in mood..after discontinuation of treatment." [10]

Wirz-Justice et al., 2011 reports on a pilot RCT of 27 pregnant women diagnosed with non-seasonal major depressive disorder. Participants were randomly assigned to 7,000 lux bright light therapy ($n = 24$) or 70 lux red dim light therapy ($n = 22$) for 1 hour per day in the morning for 5 weeks. The authors report that "the superiority of bright light over dim light placebo was shown for both SIGH-ADS ($R^2 = 0.251$; $F_{3,23} = 3.91$; $p < .05$) and HDRS ($R^2 = 0.338$; $F_{3,23} = 5.42$; $p < .01$) when analyzing the week-by-week change from baseline, and HDRS scores showed a significant interaction of treatment with time ($F_{4,92} = 2.91$; $p < .05$). Categorical analysis revealed the response rate (HDRS $\geq 50\%$ improvement) at week 5 was significantly greater for bright light (81.3%, $n = 16$) than for placebo light (45.5%, $n = 11$)($P < .05$).

Remission (final score ≤ 8) was attained by 68.8% versus 36.4%, respectively ($P < .05$).” The authors conclude that “bright white light treatment for 5 weeks improved depression during pregnancy significantly more than placebo dim red light. The study provides evidence that light therapy, a simple, cost-effective antidepressant modality with minimal side effects for the mother and no known risks for the unborn child, may be a useful non-pharmacologic approach in this difficult situation.” [11]

Wu et al., 2009 reports on a RCT of 49 adults with bipolar disorder depression (BPD.) The patients were randomized to receive chronotherapeutic treatment (CAT, $n = 32$) - which included sleep deprivation (SD,) bright light therapy (5000 lux for 2 hours for 3 consecutive days following SD,) and sleep phase advance (SPA) – or medication-only group (MED, $n = 17$.) The participants all continued to receive mood stabilizers and antidepressants. The authors report that “significant decreases in depression in the CAT versus MED patients were seen within 48 hours of SD and were sustained over a 7-week period ($t = 2.38$, $df = 64$, $p = .02$.)” The authors conclude that “this is the first study to demonstrate the benefit of adding three noninvasive circadian-related interventions to SD in medicated patients to accelerate and sustain antidepressant responses and provides a strategy for the safe, fast-acting, and sustainable treatment of BPD. “ [12]

Martiny et al., 2006 describes a RCT of 102 patients diagnosed with non-seasonal major depression, and taking the antidepressant sertraline. Patients were randomized to receive bright light therapy for 1 hour in the morning (10,000 lux, $n = 48$) or dim red light for 30 minutes in the morning (100 lux, $n = 54$) for a period of 5 weeks. This study reports on the 4 week follow-up after treatment ended {see Martiny 2004 for the original report.} The authors report that “Depression scores decreased substantially in both groups, resulting in high response and remission rates in both groups after 9 weeks of treatment. The difference in depression scores at week 5, favouring the bright-light-treated group, disappeared gradually in the 4-week follow-up period, resulting in similar end-point scores.” The authors conclude that “bright light did not have a sustained effect after discontinuation. The offset of effect was complete after 4 weeks.” [13]

Martiny, K. 2004 reports a RCT of 102 patients diagnosed with non-seasonal major depression, and taking the antidepressant sertraline. Patients were randomized to receive bright light therapy for 1 hour in the morning (10,000 lux, $n = 48$) or dim red light for 30 minutes in the morning (100 lux, $n = 54$) for a period of 5 weeks. The author reports that “...on all used scales the reduction in depression scores was larger in the bright light group than in the dim light group, and this reached statistical significance on all observer rating scales and on the SCL-90R self-assessment scale. The HAM-D6 was the most sensitive scale to measure improvement at endpoint.” The author concludes that “results support the use of bright light as an adjunct treatment to antidepressants in non-seasonal depression.” [14]

Loving et al., 2005 reports a RCT of 33 elderly patients with probable major depression. Participants were randomized to receive one hour of bright green light (1200 lux, $n = 17$) and one hour dim red light (<10 lux, $n = 16$) daily for four weeks. The authors report that “mood improved on average 23% for all subjects, but there were no significant statistical differences between treatment and placebo groups.” The authors conclude that “bright green light was not shown to have an antidepressant effect in the age group of this study, but a larger trial with brighter green light might be of value.” [15]

McEnany et al., 2005 describes a RCT of 29 women with nonseasonal, nonbipolar depression. Women were randomly assigned to either light therapy using a light visor for one hour each morning (2500 lux, a setting comparable to 10,000 lux for a light box, n = 16) or “circadian adaptation glasses” designed to filter out light (n = 13) for 28 days. The authors report that “scores on both the BDI (severity of depressed mood) and the SCL-90-Revised depression subscale (distress related to depressed mood) improved significantly in the treatment group but not in the placebo group” (F = 5.44, $df_{1,28}$, p = .02 and F = 6.23, $df_{1,28}$, p = .01.) The authors conclude that “light therapy yielded significant improvement in depression when compared with placebo intervention.” [16]

Tsai et al., 2004 reports on a RCT of 60 elderly people diagnosed with major depression or other depressive disorders. Patients were randomized to receive bright light therapy for 50 minutes in the morning (5000 lux, n = 30) for 5 days or no treatment (n = 30.) The authors report that “depressive symptoms were significantly reduced in the experimental group at post-test but no significant decline was found in the control group.” GDS scores were significantly different between the bright light therapy and control groups (mean Geriatric Depression Score of 13.2 (SD = 3.5) in the experimental group and 16.6 (SD = 4.7) in the control group, (F = 26.4, $df = 59$, p = 0.000). The authors conclude that “based upon the results of this study, light therapy could be used to decrease depressive symptoms in the elderly.”[17]

Potential for signals based on narrative comparison:

For the following outcomes, we didn’t pool the new data from two systematic reviews (SRs) (5, 6) into the meta-analyses of the original review (see reasons below) to comment on quantitative and/or qualitative signals. However, we compared the new findings against the original review’s result in a narrative manner and commented if there were potential for signals.

Reasons: We suspect the original review has a broader scope in terms of PICO elements compared with the two new SRs; however, it is still unclear why the majority of the included studies in the original review are not included in the two new SRs. Two reasons could be: 1) Al-Karawi and Jubair, 2016 limited their analyses to moderate-high quality studies; or 2) The majority of the included studies in the new two SRs are published after the publication of the original SR in 2004; however, we still do not know why some of them were not included in the edited version of the original SR published in 2010. There also exists ambiguity in terms of outcomes definition in the SRs. As such, we prefer to leave the head to head pooling of the data to the original review’s authors who have a clearer understanding of their PICO elements and eligibility criteria.

Overall Treatment effect (reduction of depression symptoms): One of the main outcomes in the original review was “depression symptom level” and the new two SRs provided data on this. Based on the original review, “The treatment response in the bright light group was better than in the control treatment group, but did not reach statistical significance..... Treatment response analyzed by primary mood rating scale endpoint scores and using a fixed effect model, was significantly better (18 studies, 505 patients, standardized mean difference (SMD) -0.20, 95% CI -0.38 to -0.01)... This finding was mainly due to the significant benefit of short term treatment of seven days or less (12 studies, 367 patients, fixed effect model: SMD-0.23, 95%CI -0.44 to -0.02). Medium term treatment did not show any

significant superiority of bright light (6 studies, 138 patients, fixed effect model: SMD -0.10, 95%CI - 0.45 to 0.24).... Since significant heterogeneity was found, the more conservative random effects model was also examined. According to the evaluation with this model, both short term studies and the total study effects were no longer statistically significant in favoring bright light over control treatment (short term studies: SMD -0.27, CI -0.64 to 0.10; total group: SMD -0.22, CI -0.52 to 0.09).". However, Perera et al., demonstrated a statistically significant beneficial effect for light therapy using a random effect model [pooled estimate from 20 RCTs (5 of which included in the original review), N= 881, SMD for post-intervention depression score -0.41 (95% CI -0.64 to -0.18)]. Similarly, Al-Karawi and Jubair, 2016 demonstrated a statistically significant results in reducing depressive symptoms after administration of bright light treatment (SMD -0.62, 95% CI -0.88, -0.35) pooling 9 moderate-high quality RCTs using a random effect model. **One Signal**

Treatment effect based on mid-term duration: Al Karawi and Jubair 2016 demonstrated significant results for mid-term exposure (1- 5 weeks) of intervention on depressive symptoms (SMD -0.78, 95% CI - 1.05, -0.51, I² 0%, random effect model) compared to the original review for mid-term effect, 1- 8 weeks, (SMD -0.10, 95% CI - 0.45, 0.24; MA# 4.2). **One Signal**

Treatment effect in studies with light intervention as monotherapy: In the original review, only two short term studies assessed monotherapy (light therapy with no co-intervention) and demonstrated a significant treatment response, evaluated by a fixed effect model (2 studies, 69 patients, SMD -0.64, 95% CI -1.14 to -0.14; forest plots was not shown) but not by a random effects model SMD -0.73, 95% CI -1.58 to 0.12; forest plots was not shown). However, Perera et al., 2016 showed significant treatment effect -SMD 0.63 (95% CI -1.00 to -0.25, P=0.001) using a random effect model (I²=60%). Similarly, Al-Karawi and Jubair 2016 demonstrated significant results for monotherapy SMD -0.71, 95% CI -1.00, - 0.43,)using a random effect model. **One Signal**

Treatment effect based on criterion of 50% decrease in depressive symptoms: In the original review there was no difference between groups (RR 0.94, 95% CI 0.61, 1.46, 3 studies, N= 71, HDRS score) treatment effect based on to the criterion of 50% decrease in depressive symptoms; however, Perera et al., 2016 demonstrated significant pooled estimate (RR 0.67, 95% CI 0.54, 0.82, 13 studies, N=276). **One Signal**

Note: for this Meta analysis, 3 of the primary studies in Perera et al., were also included in the original review (MA#2.1); however, the extracted numbers n/N slightly differed in both SRs.

Treatment effect based on higher intensity of light: The original review demonstrated non-statistically significant results (SMD -0.26, 95% CI -0.55, 0.04; 8 studies; N=198; MA#20.1) for higher intensity of bright light (>2500 lux); however, Al-Karawi and Jubair 2016 showed significant results (SMD -0.59, 95% CI -0.93, -0.25) for higher intensity (>3000 lux) bright light. **One Signal**

Treatment effect based on morning treatment: For morning light therapy, Perera et al.,2016 demonstrated similar statistically significant findings (SMD of -0.50, 95% CI -0.73 to -0.27, P<0.0001) to the original review finding(SMD -0.38, CI -0.62 to -0.14; MA#16.1) favoring treatment but with a slightly greater magnitude.

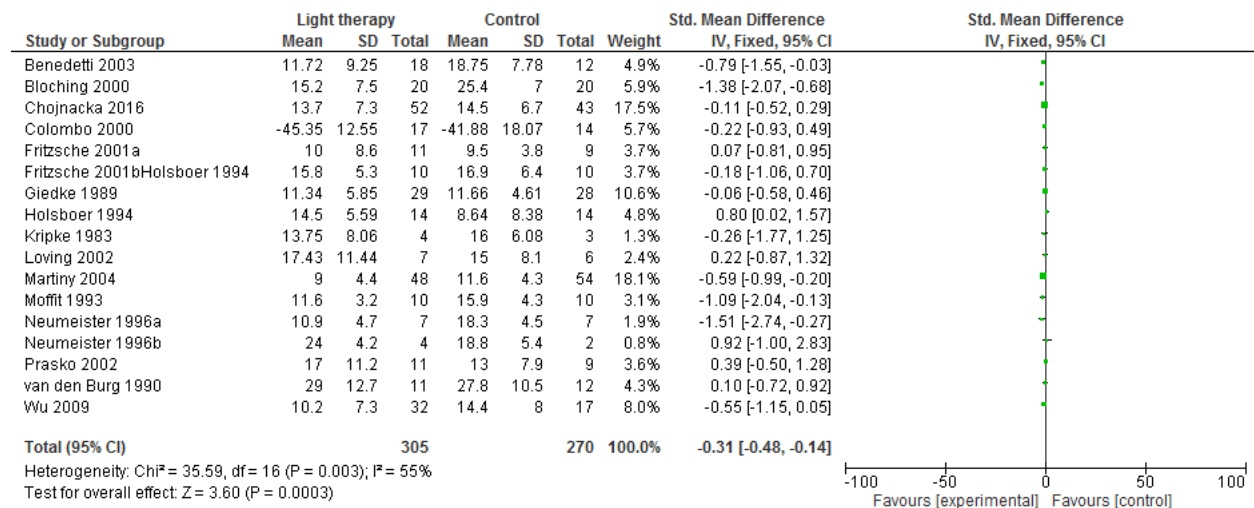
Treatment effect based on high quality studies: Similar to the original review findings for the response to bright light in high quality studies (SMD -0.90, 95% CI -1.50 to -0.31), Al-Karawi and Jubair, 2016 showed significantly significant results (SMD -0.63, 95% CI -0.84, -0.43).

Quantitative Signal:

Studies used different tools and scales to assess mood, and were usually reported for different time points. We extracted data for the endpoint score whenever it was indicated that treatment with light therapy had ended. Often, studies used multiple scales for mood rating, and we chose the primary scale for which the study reported the most detailed data. If it was unclear which scale was favoured, we took the scale that was most widely report in the original SR (e.g. Hamilton Depression Rating Scale.)

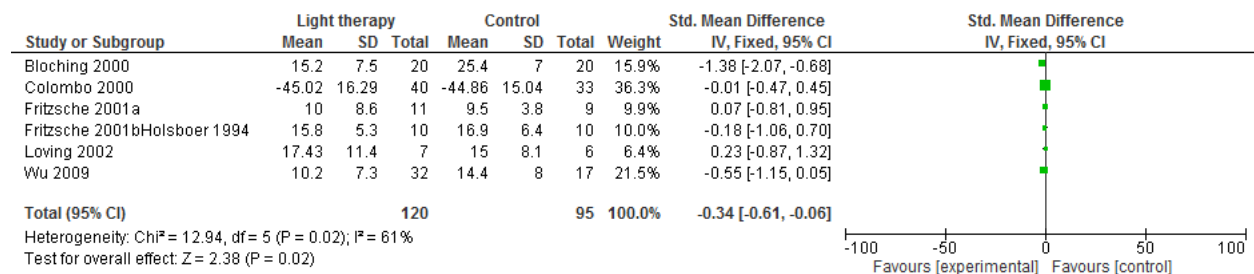
Mood rating scale (endpoint score) with concomitant drug use

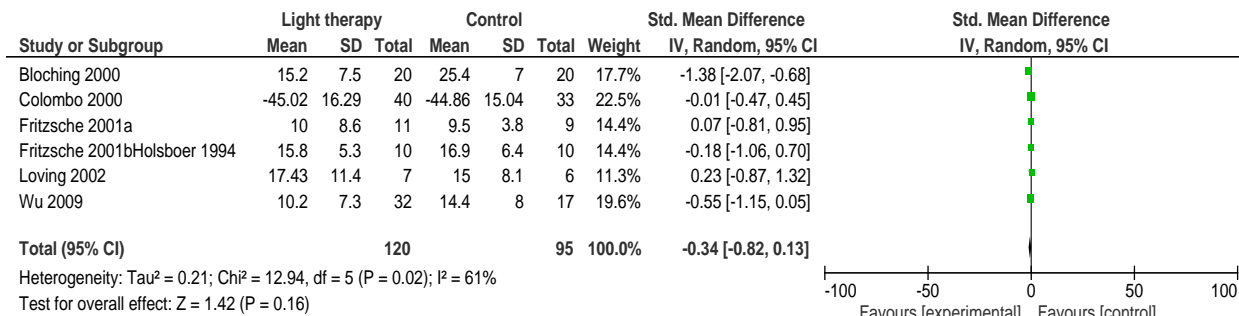
We added Chojnacka 2016, Martiny 2004 and Wu 2009 to the original review's meta-analysis. Results remained significant favouring bright light therapy (SMD -0.25, 95% CI [-0.47, -0.02], $p = 0.03$) vs. (SMD -0.31 [-0.48, -0.14])



Mood rating scale (endpint score) with concomitant SD and morning light therapy

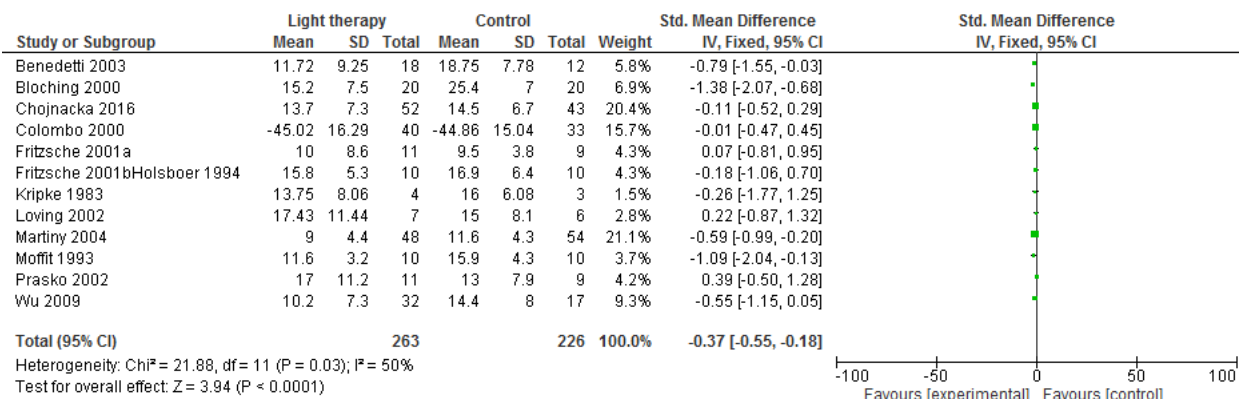
The original meta-analysis for concomitant SD and morning light therapy found a SMD of -0.28; 95% CI -0.59, 0.03. Adding Wu 2009 resulted in a SMD of -0.34; 95% CI -0.61, -0.06 favouring bright light therapy; however, the association didn't remain significant after we applied the random effect model (SMD -0.34; 95% CI -0.82, 0.13).





Mood rating scale endpoint score (concomitant drug and morning light)

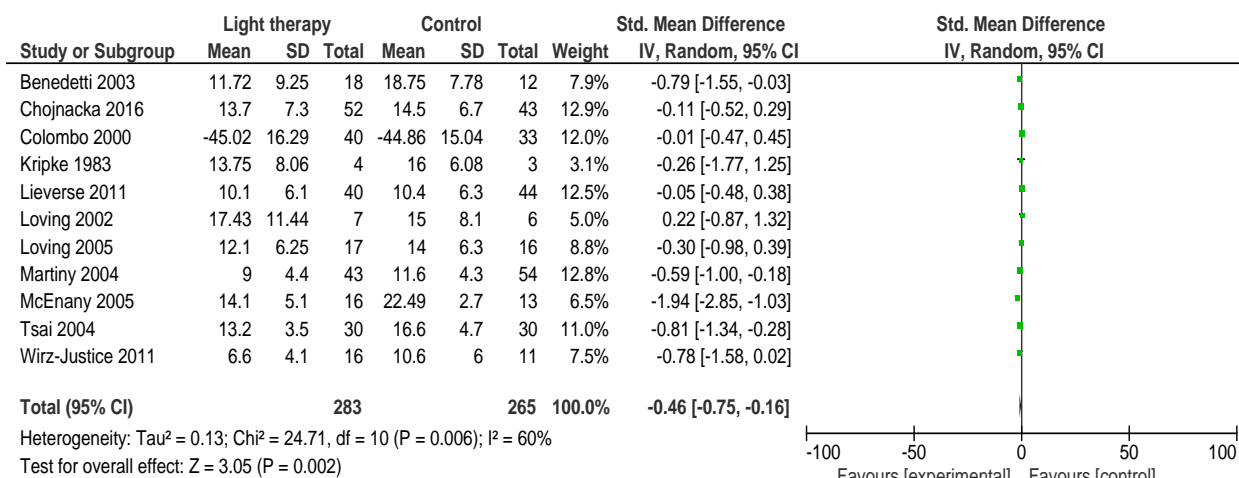
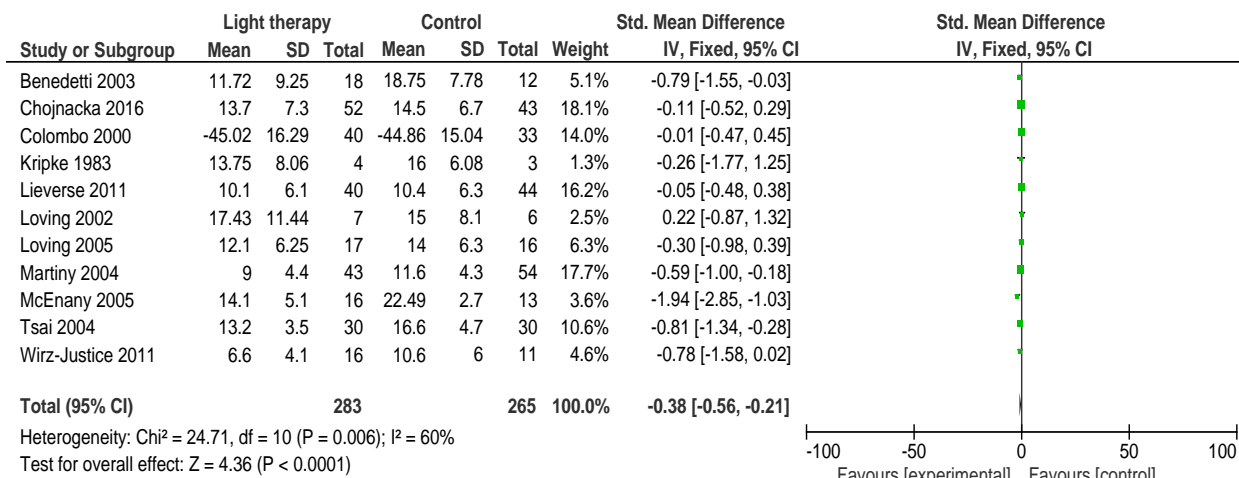
There was no difference between groups in the original meta-analysis (SMD -0.34 [-0.60, -0.08]). Adding Chojnacka 2016, Martiny 2004, and Wu 2009 did not change the results (SMD -0.37 [-0.55, -0.18])



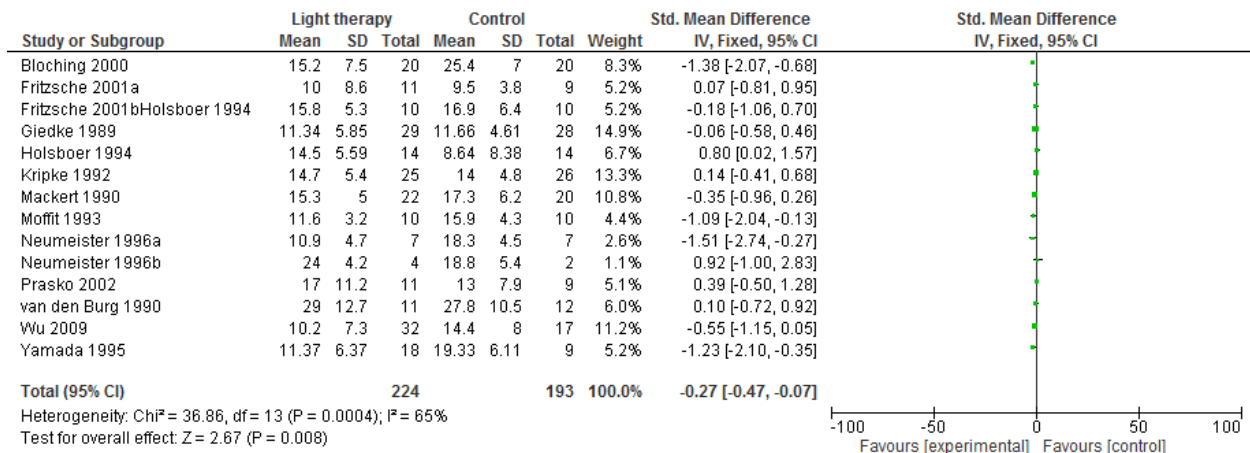
Mood rating scale endpoint score (duration of bright light)

Most of the new studies included data for bright light therapy of not more than one hour duration. The original review found no difference between the groups for duration of bright light treatment of not more than one hour (SMD -0.17 [-0.53, 0.19]; four studies, N=129).

Pooling Chojnacka 2016, Lieverse 2011, Loving 2005, Martiny 2004, McEnany 2005, Tsai 2004 and Wirz-Justice 2011 with the original meta-analysis now shows statistically significant difference favouring bright light therapy (SMD -0.38; 95% CI -0.56, -0.21; 11 studies, N=558). If we apply random effect model, the association remains statistically significant (SMD -0.46; 95% CI -0.75, -0.16). **One Signal**



The original review found that bright light therapy of more than one hour favoured bright light therapy versus control (SMD -0.24 ; 95% CI -0.45, -0.03) Adding Wu 2009 did not change results (SMD -0.27 ; 95% CI -0.47, -0.07)



Adverse effects:

The original review includes a meta-analysis pertaining to “acceptability of treatment” which they define as “number of persons dropping out.” However, it is unclear whether the patients have dropped out due to only adverse effects, or if this is the total number of drop-outs. As such, we were unable to pool drop-out data from the new studies.

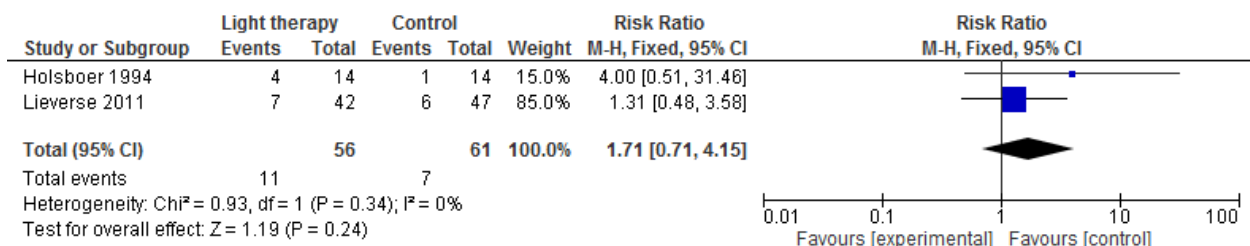
In Martiny 2004, 2/53 patients in the bright light treatment group withdrew due to side effects, compared to 0/54 patients in the control group. Chojnacka 2016 reported a total of 3 dropouts due to side effects, but did not report whether these participants had been receiving BLT or placebo.

Lam 2015 also reported drop-outs due to adverse events, including 1/32 in the placebo group, 2/21 in the drug treatment group, 1/32 in the bright light therapy group and 1/29 in the combined BLT and drug treatment group. There was no significant difference between conditions in dropout rates due to adverse effects.

The following analyses for adverse effects were conducted by pooling data from new studies with the original review’s meta-analyses. None generated a signal.

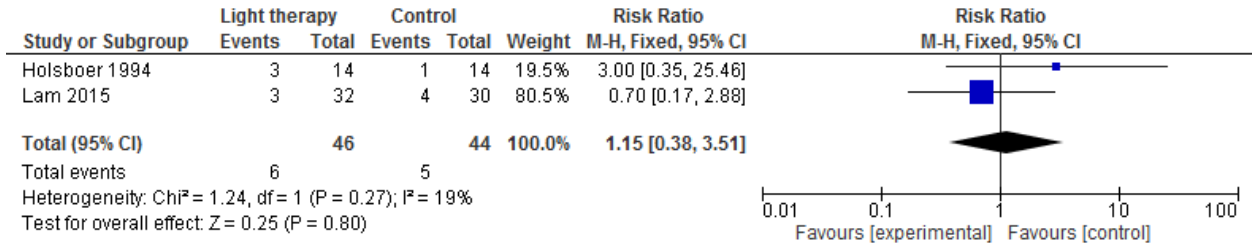
1) Sweating; original review meta-analysis: RR, M-H Fixed 4.00, 95% CI [0.51, 31.46]

One study (Lieverse 2001) was added to the meta-analysis resulting in a RR (M-H fixed) of 1.71, 95% CI [0.71, 4.15]



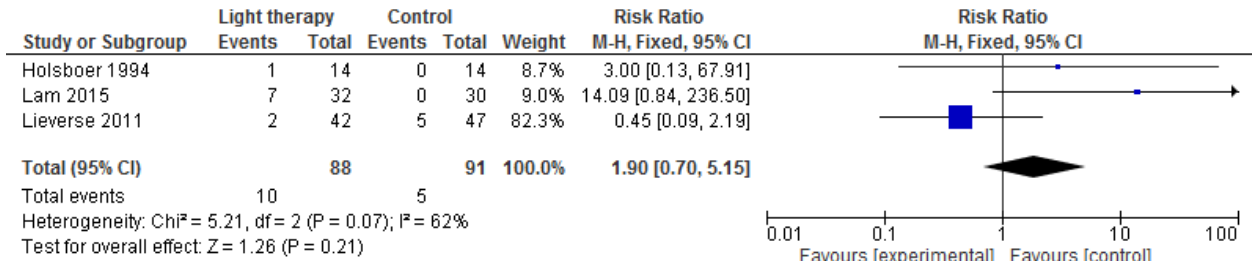
2) Decreased appetite; original review meta-analysis: RR (M-H Fixed) 3.00, 95% CI 0.35, 25.46

One study (Lam 2015) was added to the meta-analysis resulting in a RR (M-H fixed) of 1.15, 95% CI 0.38, 3.51.



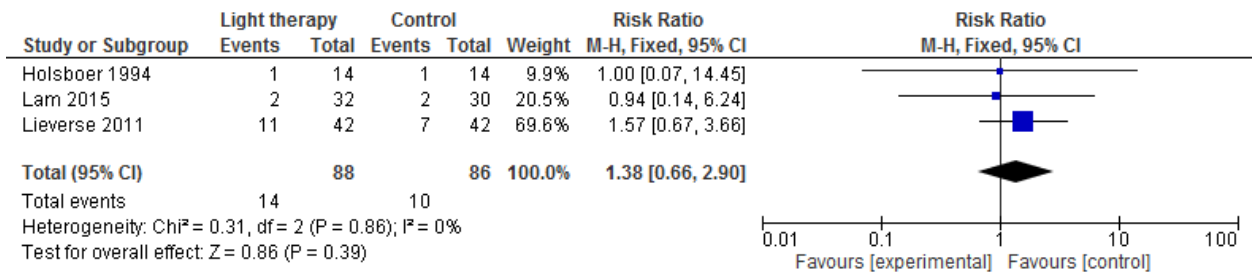
3) Diarrhea; original review meta-analysis: RR (M-H Fixed) 3.00, 95% CI [0.13, 67.91]

Two studies (Lam 2015 and Lieverse 2011) were added to the meta-analysis resulting in a RR (M-H fixed) of 1.90, 95% CI [0.70, 5.15]



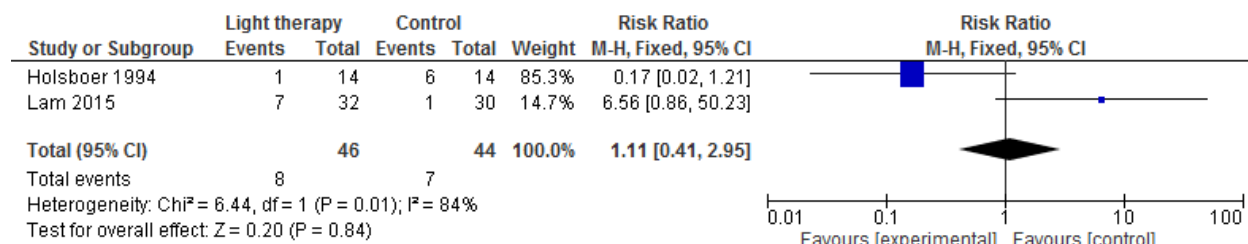
4) Dry mouth; original review meta-analysis: RR, M-H Fixed 1.00, 95% CI [0.07, 14.45]

Two studies (Lam 2015 and Lieverse 2011) were added to the meta-analysis resulting in a RR (M-H fixed) of 1.38, 95% CI [0.66, 2.90]



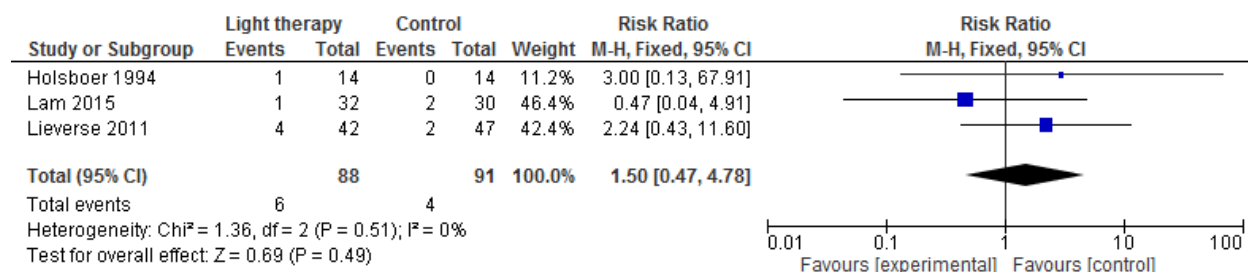
5) Increased appetite; original review meta-analysis: RR (M-H Fixed) 0.17, 95% CI [0.02, 1.21]

One study (Lam 2015) was added to the meta-analysis resulting in a RR (M-H fixed) of: 1.11, 95% CI [0.41, 2.95]



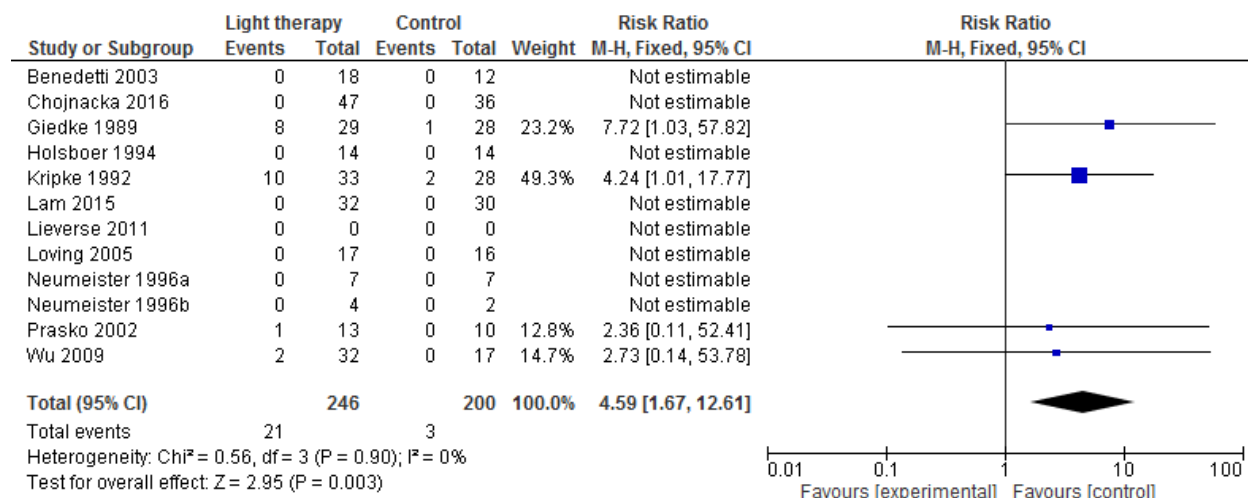
6) **Nausea**; original review meta-analysis: RR, M-H Fixed 3.00, 95% CI [0.13, 67.91]

Two studies (Lam 2015 and Lieveise 2011) were added to the meta-analysis resulting in a RR (M-H fixed) of 1.50, 95% CI [0.47, 4.78]



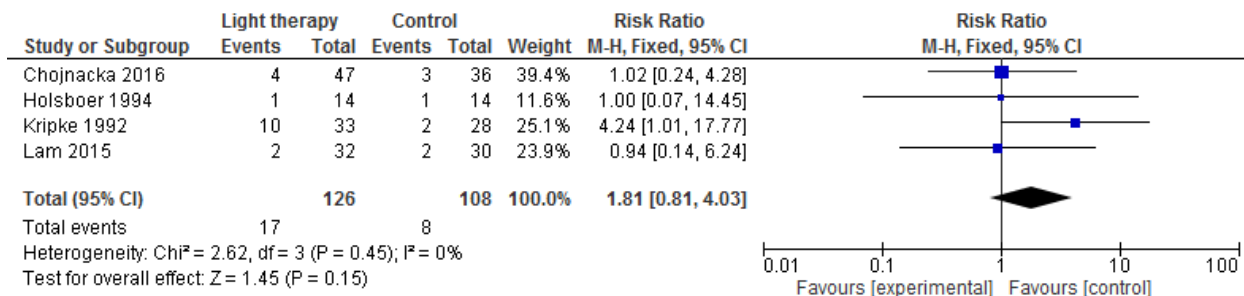
7) **Hypomania**; original review meta-analysis: RR (M-H Fixed) 4.91, 95% [1.66, 14.46]

Four studies (Chojnacka 2016, Lam 2015, Loving 2005 and Wu 2009) were added to the meta-analysis resulting in a RR (M-H fixed) of 4.59, 95% CI [1.67, 12.61]



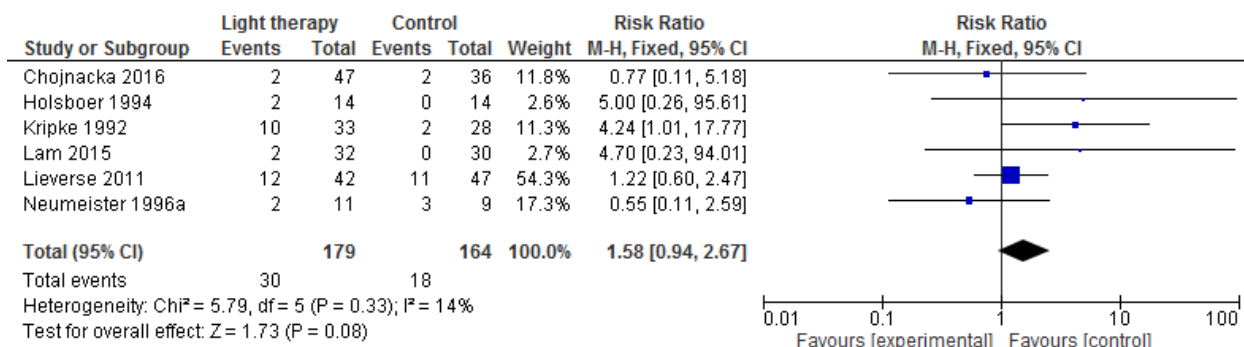
8) **Agitation**; original meta-analysis: RR (M-H Fixed) 3.22, 95% CI [0.95, 10.89]

Two studies (Chojnacka 2016 and Lam 2015) were added to the meta-analysis resulting in a RR (M-H fixed) of 1.81, 95% CI [0.81, 4.03]



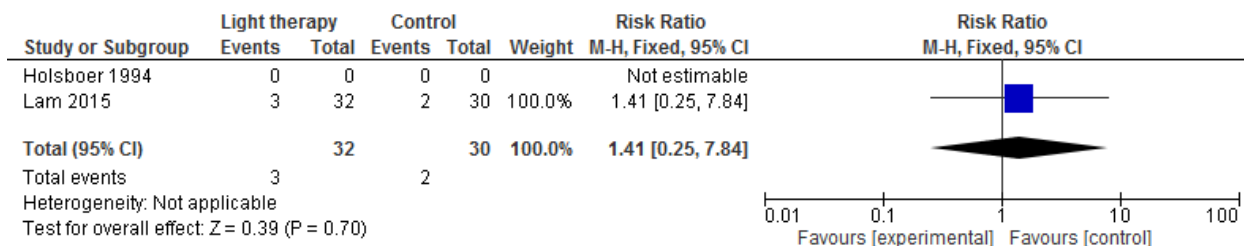
9) **Headache**; original meta-analysis: RR (M-H Fixed) 2.26, 95% CI [0.91, 5.59]

Three studies (Chojnacka 2016, Lam 2015 and Lieveise 2011) were added to the meta-analysis resulting in a RR (M-H fixed) of: 1.58, 95% CI [0.94, 2.67]



10) **Disturbed sleep**; original meta-analysis: RR (M-H Fixed) not estimable

One study (Lam 2015) was added to the meta-analysis resulting in a RR (M-H fixed) of 1.41, 95% CI [0.25, 7.84]



Conclusion: One quantitative signal in addition to five potential quantitative signals (based on our narrative comparison) were generated. As such, some of the conclusions in the original review may need updating.

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Appendix A: Overview of the Modified Ottawa Method

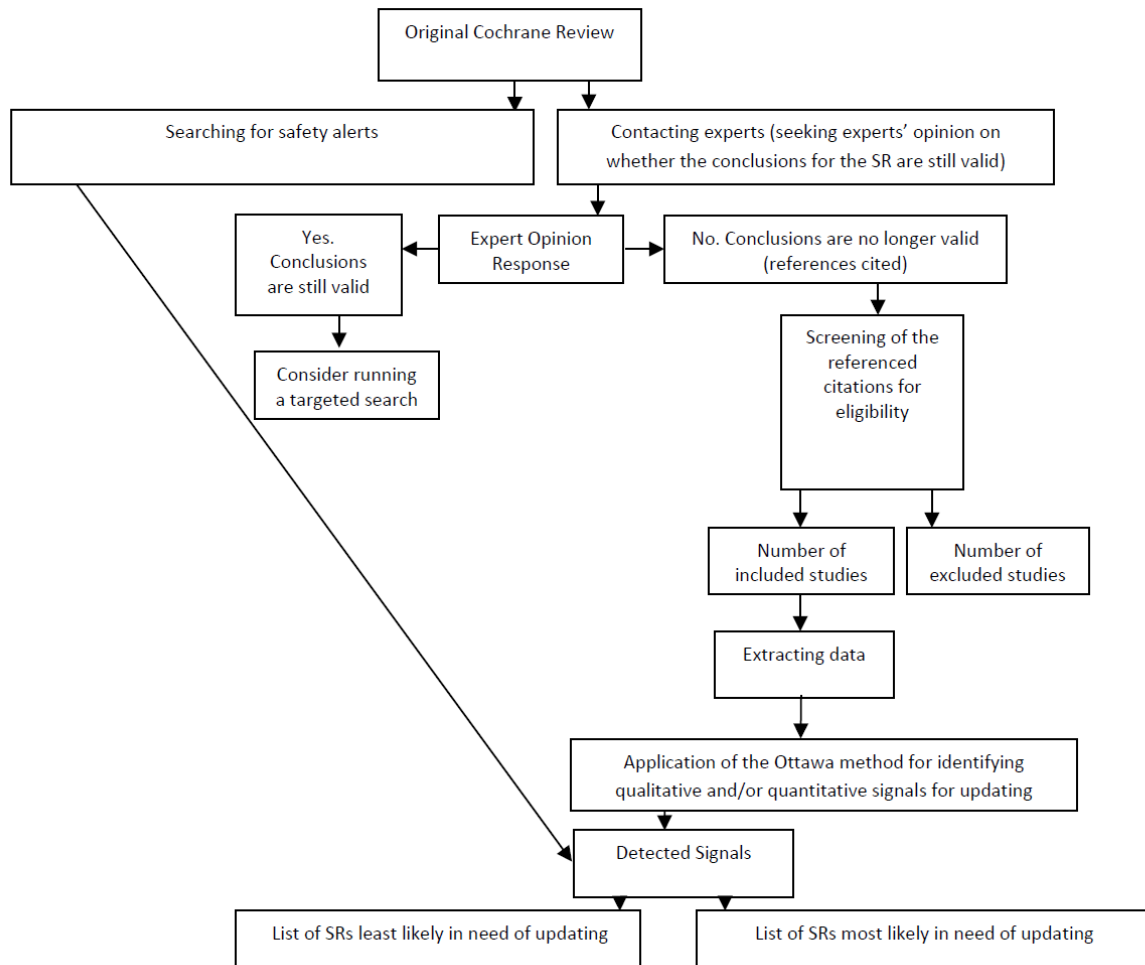


Figure 1: The process of signal detection methods for Cochrane reviews

Appendix B: Expert Opinion Survey

Conclusions from systematic review	Is the conclusion(s) in this review still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in this review? (Yes/No/Don't know) If yes, please provide references	Comments
<p>Review Objective: To evaluate clinical effects of light therapy in comparison to the inactive placebo treatment for non-seasonal major depressive disorder, dysthymia, minor depression, bipolar disorder, and other depressive conditions.</p>			
<p>Overall Conclusion of the Review: For patients suffering from non-seasonal depression, light therapy offers modest though promising anti depressive efficacy, especially when administered during the first week of treatment, in the morning, and as an adjunctive treatment to sleep deprivation responders. Hypomania as a potential adverse effect needs to be considered. Due to limited data and heterogeneity of studies these results need to be interpreted with caution.</p> <p><u>Further Details:</u> Twenty studies (49 reports) were included in the review. Most of the studies applied bright light as adjunctive treatment to drug therapy, sleep deprivation, or both. In general, the quality of reporting was poor, and many reviews did not report adverse effects systematically. The treatment response in the bright light group was better than in the control treatment group, but did not reach statistical significance. The result was mainly based on studies of less than 8 days of treatment, which might indicate a more rapid action than with antidepressant drugs. A wide range of durations and intensities of bright light</p>			

<p>were applied. High versus low daily duration and intensity of light did not show any superiority over each other. It also needs to be remembered that previous research has shown that these variables are interrelated and possibly confounding, i.e., the higher the intensity, the shorter the duration is effective. The review covered all forms of non-seasonal depression. The benefit of bright light in specific forms of depression and in various age groups was not possible to evaluate sufficiently. In particular, there was an absence of RCTs for more than four weeks of treatment.</p>			
<p>Global State: Continuous CGI endpoint scores showed that, based on a small medium term study (Prasko 2002), there was a trend for the control treatment being more effective than bright light.</p>			
<p>*Please note that authors are reporting both fixed effect and random effect models. Please respond “yes/no/don’t know” where appropriate.</p> <p>Mental State:* - Treatment response, analyzed by primary mood rating scale endpoint scores and using a fixed effect model, was significantly better in the bright light group compared to the control treatment group (18 studies, 505 patients, standardized mean difference (SMD) - 0.20, CI -0.38 to -0.01). A negative standardized mean difference means that the bright light group was better than the control group. This finding was mainly due to the significant benefit of short term treatment of seven days or less (12 studies, 367 patients, fixed effect model: SMD-0.23,CI -0.44 to -0.02). Medium term treatment did not show any significant superiority of bright light (6 studies, 138 patients, fixed effect model:</p>			

<p>SMD -0.10, CI -0.45 to 0.24).</p> <p>- Since significant heterogeneity was found, and the more conservative random effects model was also examined. According to the evaluation with this model, both short term studies and the total study effects were no longer statistically significant in favoring bright light over control treatment (short term studies: SMD -0.27, CI -0.64 to 0.10; total group: SMD -0.22, CI -0.52 to 0.09).</p> <p>- Six studies in which the change score data of primary mood rating scales including SDs were available (Kripke 1983; Kripke 1987; Kripke 1992; Bloching 2000; Colombo 2000; Loving 2002) were also significantly in favor of bright light based on a fixed effect model but not based on a random effects model (6 studies, 198 patients; fixed effect model: SMD -0.35, CI -0.64 to -0.06; random effects model: SMD -0.46, CI -1.10 to 0.18). More conservative evaluation using the random effects model was in line with previous comparisons but statistical significance was lost (short term: SMD -0.40, CI -0.90 to 0.10, the total group: SMD -0.23, CI -0.61 to 0.15). In self-rated responses, the treatment effects of bright light and control treatments were close to equal with a fixed effect model approach (short term studies: 9 studies, 320 patients, SMD -0.02, CI -0.24 to 0.20; medium term studies: 3 studies, 68 patients, SMD -0.11, CI -0.60 to 0.37; total group: 12 studies, 388 patients, SMD -0.04, CI -0.24 to 0.17).</p> <p>- There were only two short term studies (Mackert 1990; Yamada 1995) that had applied bright light only, i.e. the patients were not exposed to sleep deprivation</p>			
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<p>or other adjunctive treatments and did not receive any medication. The treatment response, evaluated by a fixed effect model, was better for bright light than for control treatment (2 studies, 69 patients, SMD -0.64, CI -1.14 to -0.14). With a more conservative random effects model the result was in line with a fixed effect model approach but did not reach statistical significance (SMD -0.73, CI -1.58 to 0.12).</p> <p>- According to the criterion of 50% decrease in the HDRS score, there was no difference between groups: 20 out of 39 patients (51%) in the bright light group and 17 out of 32 patients (53%) in the control treatment group were not improved (3 studies, 71 patients, relative risk (RR) 0.94, CI 0.61 to 1.46). One study (Prasko 2002) used a more conservative criterion of the definition of improvement (50% improvement and a score less than 8). In their study sample 9 out of 13 patients (69%) in the bright light group and 7 out of 10 patients (70%) in the control treatment group were not improved.</p> <p>- Only a few short term studies (Yamada 1995; Colombo 2000; Loving 2002) had analyzed the deterioration in mental state or relapse of the participants during treatment. These studies showed a trend of the occurrence of less deterioration/relapses in the bright light group compared to findings in the control treatment group, but the result was not statistically significant (3 studies, 120 patients, RR 0.40, CI 0.12 to 1.31). None of the medium term studies provided information on this outcome.</p>			
<p>Adverse Effects: One study that used concomitant trimipramine drug treatment reported on adverse effects in detail (Holsboer 1994), and several other studies gave short</p>			

<p>notes on adverse effects during the study. Six studies gave information on the occurrence of mania, and in the only study that had detected patients suffering from mania (Colombo 2000), the condition was more frequent in the control treatment group. Evaluation of hypomania was reported in seven studies, in which 19 out of 118 participants in the bright light group and 3 out of 101 patients in the control group developed hypomania (7 studies, 219 patients, RR 4.91, CI 1.66 to 14.46, number needed to harm (NNH) 8, CI 5 to 20). It needs to be acknowledged that categorizing the drop-out subjects as “failures” might overestimate the number of subjects with this adverse effect as well as with other poor outcomes. Headache was slightly more frequent in the bright light group compared to control treatment group, but did not reach statistical significance (3 studies, 109 patients, RR 2.26, CI 0.91 to 5.59). None of the patients had experienced disturbed sleep. Sleep onset difficulties were more frequent in the bright light group, although this information was reported in one study only (Kripke 1992). Agitation, headache, blurred vision and eye irritation were slightly though statistically non-significantly more common in the bright light group than in the control group (agitation: 2 studies, 89 patients, RR 3.22, CI 0.95 to 10.89; headache: 2 studies, 109 patients, RR 2.26, CI 0.9 to 5.59; blurred vision: 2 studies, 89 patients, RR 2.22, CI 0.73 to 6.78; eye irritation: 2 studies, 68 patients, RR 3.53, CI 0.97 to 12.88). Other isolated adverse effects did not show any preference over either of the treatment groups. Two studies (Mackert 1990; Holsboer 1994) had applied a structured symptom scale for adverse effects: the short term study (Mackert 1990) did not find any significant difference between</p>			
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<p>treatment groups, whereas the medium term study (Holsboer 1994) showed slightly but not statistically significantly more adverse effects in the bright light group than in the control treatment group.</p>			
<p>Acceptability of Treatment: Acceptability of treatment, analyzed by the number of patients dropping out of the study, did not show any significant difference between the groups (16 studies, 453 patients, RR 1.35, CI 0.60 to 3.07).</p>			
<p>Quality of Life, cost effectiveness and follow-up: These issues were not evaluated in the included studies. Follow up of the mood scores was evaluated in 5 studies only (Giedke 1989; van den Burg 1990;Kripke 1992;Holsboer 1994; Benedetti 2003) and it was short (between 2 days and 2 weeks).These studies did not show any statistically significant superiority of bright light over control treatment (5 studies, 189 patients, SMD 0.15, CI -0.14 to 0.44).</p>			
<p>Mortality: No mention of mortality or permanent injuries was made in any of the studies. The studies in which all the participants had completed an assigned treatment enabled us to conclude indirectly that no deaths occurred.</p>			
<p>Subgroup Analyses: Concomitant sleep deprivation: Treatment responses between studies with patients who underwent sleep deprivation and those who did not showed that with a fixed effect model approach sleep deprivation studies showed a non-significant trend to favor for bright light over control treatment (9 studies, 266 patients, SMD - 0.22, CI -0.47 to 0.22), whereas in studies without sleep deprivation bright light was significantly better than control treatment (6 studies, 167 patients, SMD -</p>			

<p>0.34, -0.66 to -0.02). When a random effects model was applied with the latter group, the significance was lost (SMD -0.36, CI -0.99 to 0.26). If patients were awakened 1-to-2 hours before wake-up time, there was no difference between bright light and control treatment groups based on a fixed effect model approach (2 studies, 21 patients, SMD 0.39, CI -0.50 to 1.28).</p> <p>In studies in which both bright light and sleep deprivation were applied, a fixed model approach revealed that the sleep deprivation responders had a statistically significantly better response to bright light than to control treatment (4 studies, 63 patients, SMD -1.02, CI -1.60 to -0.45). The result remained significant even though a more conservative random effects model was applied (SMD -1.24, CI -2.45 to -0.03). This finding was mainly due to short term studies (a fixed effect model approach: 3 studies, 43 patients, SMD -1.84, CI -2.60 to -1.07), and remained statistically significant even when a random effects model was applied (SMD -1.84, CI -2.60 to -1.07). In a medium term study there was no difference in response between bright light and control treatments (1 study, 20 patients, SMD 0.07, CI -0.81 to 0.95). The sleep deprivation non-responders showed no significant difference in response between bright light and control treatments according to a fixed model approach (3 studies, 45 patients, SMD -0.25, CI -0.85 to 0.36).</p> <p>Concomitant drug treatment: great majority of studies had applied concomitant drug treatment (14 studies, 329 patients) whereas only a few studies had no drug treatment (4 studies, 134 patients). Evaluation of concomitant drug therapy showed that in studies with</p>			
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<p>patients receiving concomitant pharmacotherapy, bright light showed a statistically significant efficacy over control treatment with a fixed effect model approach (14 studies, 329 patients, SMD -0.25, CI -0.47 to -0.02), but significance was lost when a random effects model was applied (SMD -0.24, CI -0.61 to 0.12). Studies with patients not receiving concomitant drug therapy showed a statistically non significant trend of response to bright light over control treatment (4 studies, 134 patients, SMD -0.18, CI -0.53 to 0.17).</p> <p>Time of day of bright light therapy: The time of the day for bright light treatment was evaluated by categorizing the studies into the following groups: morning light (11 studies, 297 patients), evening light (2 studies, 43 patients), all-night light (2 studies, 80 patients), both morning and evening light (2 studies, 20 patients), and various times of light treatment (2 studies, 65 patients). Based on a fixed effect model approach, the effect of morning light was statistically significantly better than that of control treatment (11 studies, 297 patients, SMD-0.38, CI -0.62 to -0.14), whereas the treatment administered at other times of the day didn't show any superiority over control treatment. Even with a more conservative random effects model the response to morning light treatment remained statistically significantly better than the response to the control treatment (SMD -0.43, CI -0.82 to -0.05). When the combination of concomitant sleep deprivation and morning bright light were evaluated, the treatment response with morning light plus concomitant sleep deprivation showed a statistically non-significant trend for bright light over control treatment based on a fixed model approach (5 studies,</p>			
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<p>166 patients, SMD -0.28, SMD -0.59 to 0.03). Using the same fixed effect model, morning light without concomitant sleep deprivation was statistically significantly more effective than control treatment (5 studies, 124 patients, SMD -0.53, CI -0.91 to -0.16), and the result remained statistically significant even when a more conservative random effects model was applied (SMD -0.62, CI -1.24 to -0.01).</p> <p>A combination of concomitant drug therapy and morning light was applied in half of the studies (9 studies, 243 patients), whereas morning light without any drug therapy was rare (2 studies, 54 patients). Evaluation of the effect of combination of concomitant drug and morning bright light showed that there was no difference between the two morning light conditions with or without pharmacotherapy.</p> <p>With a fixed effect model approach, both conditions were statistically significantly in favor of bright light over control treatment (combination treatment: 9 studies, 243 patients, SMD -0.32, CI -0.60 to -0.08; light only: 2 studies, 54 patients, SMD -0.57, CI -1.14 to -0.01), but with a more conservative random effects model the statistical significance was lost (combination treatment: SMD-0.36, CI -0.79 to 0.07; light only: SMD-1.03, -2.63 to 0.58).</p> <p>Device: The majority of studies had used a light box (12 studies, 275 patients) whereas another device was used in only a few studies (5 studies, 157 patients). In studies using a light box, a fixed effect model approach showed that bright light was more effective than the control treatment (12 studies, 275 patients, SMD -0.50, CI -0.75 to -0.25), and the statistical significance remained</p>			
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<p>even when a random effects model was applied (SMD - 0.47, CI -0.86 to -0.08). If other devices, e.g. lighted rooms, were used, there was a trend for control treatment being better than light treatment but the result did not reach statistical significance (5 studies, 157 patients, SMD 0.21, CI -0.11 to 0.52).</p> <p>Intensity of bright light: There was no difference in contrasts between bright light and control treatment groups in terms of intensity of bright light (more than 2500 lux: 8 studies, 198 patients; 2500 lux maximum: 8 studies, 133 patients) or duration of light exposure (more than one hour: 13 studies, 368 patients; one hour or less: 4 studies, 123 patients).</p>			
<p>Abbreviations: CGI = Clinical Global Impressions; SMD = standardized mean difference</p>			

Appendix C: The Ottawa Method Qualitative Signals*

Potentially invalidating change in evidence

This refers to a situation in which it is expected that clinicians do not act upon the results of the original systematic review (SR) and the agency/organization that supported the original production of the SR would retract the SR until it is updated. Criteria for potentially invalidating change in evidence are presented below.

This category of signals (A1-A3) specifies findings from a pivotal trial**, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of “opposing findings” – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

* Please, see Shojania et al. 2007 for further definitions and details

**A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

Appendix D: Modified PRESS Review for Original Review's Search Strategy

The original search was performed in January 2003 and does not appear to have been updated since then. It was performed in the Depression Anxiety and Neurosis Controlled Trial register, which searches multiple databases for randomized controlled trials. There is no detailed strategy in an appendix, although all Cochrane registers have developed sensitive strategies specific to their review group which can be accessed elsewhere.

The light therapy concept is expressed minimally in the search, and is comprised of only two terms, "phototherapy" or "light therapy". A useful addition would have been the MeSH "Light" with the subheading "therapeutic use", which was used to index MEDLINE records from 1967 to 1980. Other possibilities for vocabulary include heliotherapy, sunlight therapy/treatment, and ultraviolet or UV therapy. As well, applying truncation to the existing words would have picked up plural and other word forms, and the use of proximity operators could have been used to pick up variations such as therapeutic light or therapeutic sunlight.

In conclusion, the strategy has limitations both with regard to vocabulary and documentation, and potentially relevant citations may have been missed.

Appendix E : Excluded references at full text

Agargun, M, Sayar, G, Bulut, H and Tan, O. Comparison of effects of bright light therapy alone or combined with fluoxetine on severity of depression, circadian rhythms, mood disturbance, and sleep quality, in patients with non-seasonal depression. 2013, *ChronoPhysiology and Therapy* 2013:3 53–59.

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